REMARKS

1. General Matters

1.1. An amendment after final rejection was filed on January 5, 2005. This amendment submitted a new sequence listing, a corrected Fig. 3, and various amendments to the claims. The February 9, 2005 advisory action entered the sequence listing and the amended drawing, but not the claim amendments.

The instant amendment duplicates certain of the claim amendments which were refused entry on the ground that they allegedly raise new issues which would require further consideration. Hence, if the first action after the RCE is a rejection, it would not be proper to make it "final". See MPEP 706.07(b).

We thank the Examiner for critiquing the amendment after final; we have taken the Examiner's comments into account. In order to make it easier for the Examiner to determine which portions of the Remarks are new, we have set the new text in italics. Note that certain sections have been renumbered.

In response to section 5 of the advisory action, we wish to point out that Clause (iii) has been deleted.

We discuss sections 6 and 7 of the Advisory Action later in these remarks. However, we think it appropriate to mention here that new claim 102 is prompted by the statement (middle of page 4 of the Advisory Action) that "the limitations recited in i)-iii) are not required for the polypeptide being claimed".

References of "OA" are to the original office action, mailed September 7, 2004.

1.2. Claims 17, 85 and 94 have been cancelled, claims 101-*107* have been added, and various claims have been amended. The limitations of claim 94 have been incorporated into claim 90.

1.3. We have addressed all of the claims objections (claims 17, 90, 92, 93, 95, 100) in the manner recommended by the Examiner, except that we refer to the polypeptide of SEQ ID NO:2 in claim 93. SEQ ID NO:1 is a nucleotide sequence.

1.4. Claim 12 previously covered SEQ ID NO:2 per se via 12(a). This has been excised, so (b) became (a). SEQ ID NO:2 is still covered by claim 99.

Paragraphs (c) and (d) have been excised, so (e) become (b). Please note that in view of our interpretation of percentage identity, a sequence 99% identical to (a) could differ from (a), not only by substitutions, but also by insertions or deletions. This is made explicit in amended 12, paragraph (b). Note that there can be insertions and deletions and substitutions, if desired.[1] Since sequence (a) is 1558 amino acids, and 1% of 1558 is 15.58, a polypeptide cannot exhibit more than 15 such differences from 12(a), and still be within 12(b).

New claim 102 is similar to amended claim 12, but omits the activity limitations. New claim 103 requires that the polypeptide have proteolytic activity against IGFBP-5. New claim 104 limits claim 12 to mature PAPP-A2 and substitution mutants thereof. New claim 105 limits the length of insertions or deletions, based on P42, L4-7 and P43, L33-P44, L9. New claim 106 limits insertions or deletions to the N- and C-terminal regions, per P43, L33-P44, L9. New claim 107 combines these limitations. New claim 108 limits 12 to polypeptides which are fragments of mature PAPP-A2 (i.e., no amino acid substitutions, just N- or C-truncations). Claim 70 was cancelled in favor of new claim 109 which, like 102, omits the activity limitations.

2. Indefiniteness Rejections (OA §§5-10)

Claims 17, 93, 95 and 100 stand rejected for indefiniteness. *OA §§5-6 quote the statute, and the conclusion, while the specific rejections are in §§7-10.*

2.1. (OA §7). The mature PAPP-A2 sequence is defined at P43, L34 as being AAs 234-1791 of SEQ ID NO:2. The prepro part of PAPP-A2 is defined at P44, L16-17 as being AAs 1-233 of SEQ ID NO:2. Claim 17 has been cancelled. *Claim 99 recites amino*

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[1] Insertions and deletions may be internal, or at the N- or C-ends, cp. claim 106.

acids 1-233 directly, without using the "prepro part" terminology.

SEQ ID NO:2 itself is most precisely referred to as a preproPAPP-A2 (P10, L7-8). *The term "PAPP-A2", when used without qualification in the context of a therapeutic or diagnostic entity, as in claim 30, refers to mature PAPP-A2.*

2.2. *(OA §8).* Claim 93 has been amended in accordance with the Examiner's interpretation, i.e., it comprises at least 1169 consecutive amino acids of the "fragment" 234-1791 of SEQ ID NO:2. We don't agree with all of the Examiner's comments in OA §8. Specifically, we don't agree that an 1169 a.a. fragment can be considered 100% identical to a 1558 a.a. protein, even if they are identical in the aligned region.

2.3. *(OA §9).* *Applicants* first note that the positions of consensus sequences LNR1, LNR2, LNR3, SCR1, SCR2, SCR3, SCR4 and SCR5, as well as of the elongated zinc finger binding consensus sequence, were plainly identified in the original disclosure by P52, L3-10, P57, L17-22, and Fig. 3. We pointed this out in the paragraph bridging pages 11-12 of the last response, and hence there was no justification for the Examiner deeming to give "no patentable weight" to these limitations of claim 95.

As suggested by the Examiner, we have amended claim 95 to identify, for each consensus sequence, its location within SEQ ID NO:2 as determined by reference to Fig. 3.

2.4. (OA §10). This rejects claim 100 because "processing variant" is allegedly indefinite. The examiner interpreted the processing variants as those "resulting from intracellular proteolysis". Claim 100 has been amended to make this explicit.

3. Written Description *(OA §§11-15)*

3.1. Claims 90-91, 93 and 95 stand rejected for allegedly failing to comply with the written description requirement.

The Examiner questions four limitations of the claims:

(1) a fragment of at least 6 amino acids of residues 234-1791 of SEQ ID NO:2 (claim 90);

(2) a fusion protein comprising amino acids 234-1791 of SEQ ID NO:2 where said fusion is not a pregnancy associated plasma protein (claim 90);
(3) a fragment of at least 1196 [sic, 1169] consecutive residues of residues 234-1791 of SEQ ID NO:2 (claim 93); and
(4) a consensus sequence labeled LNR-3 (claim 95).

With respect to limitation (1), claim 90 now recites that the fragment is at least 5 amino acids long, for which basis exists at P7, L14. There is also explicit basis for at least 7, 9, 10, 11, 12, 13 or 17 amino acids, see P7, L14-15. At least 17 amino acids is recited in claim 92.

Turning to limitation (2), the proviso that the fusion protein is not a PAPP has been excised. Support for fusion proteins in general appears at P7, L19, P14, L17-22, P15, L29-P16, L10, P17, L27-28.

With regard to limitation (3), P35, L11 recited variants having at least 75% amino acid sequence identity with PAPP-A2. Mature PAPP-A2 totals 1558 residues, and 75% of 1558 is 1168.5, which rounds to 1169. Hence, there is basis for claim 93.

Finally, point (4) complains that LNR3 is not identified in Fig. 3. It was clearly applicants' intent to recognize an LNR3 within Fig. 3 (P52, L6), at a location analogous to the LNR3 region of PAPP-A as identified in Kristensen, et al., 1994, biochemistry, 33, 1592-8 (P52, L4). *As pointed out above in the amendment after final rejection, LNR3 was mislabeled as "LNR1" in Fig. 3; amended Fig. 3 has been entered by the Examiner.*

3.2. Claims 12, 18-19, 75, 83 and 97-99 are also rejected for alleged noncompliance with the written description requirement. It appears that OA §§13-15 reject these claims because (1) of the alternative functional limitations of claim 12, and (2) the lack of any functional limitation in claims 97-99. *(We hope the Examiner will appreciate that there is some inconsistency between these two positions.)*

3.2.1. Taking up claims 97-99, first, these claims related to the prepro part, which does not itself confer any PAPP-A2-like activity. Claims 97-99 have been amended to recite the presence of the mature PAPP-A2 and certain mutants of same, in a manner paralleling claim 12. Thus, claims 97-99 are drawn to precursors of mature PAPP-A2 *and certain variants thereof*.

Claims 97-99 have been amended to make this clear, *and they now have the functional limitations of claim 12.*

3.2.2. With regard to claim 12, all of the alternative functions recited in claim 12 are explicitly taught in the original claim 12 of the specification, and hence are considered part of the description. See In re Koller, 613 F.2d 819, 204 USPQ 702 (CCPA 1980). *They are also taught at page 32, lines 10-20 of the specification.*

We have amended claim 12 to make it clear that activity ii) refers to mature PAPP-A2 (234-1791 of SEQ ID NO:2). Activity iii) is no longer recited.

Mature PAPP-A2 (amino acids 234-1791 of SEQ ID NO:2) is representative of

(i) the claimed polypeptides with activity (i), *and*

(ii) the claimed polypeptides with activity (ii).

For each of these activities (i) and (ii) the claimed genus falls within the safe haven (at least 95% identity) set forth in the Written Description Training Materials, Example 14.

We would also point out that while there are no other specifically disclosed mutants, there are several specifically disclosed species, notably 234-1791 (mature PAPP-A2, P43, L33-34), the processing variant 200-1791 (P43, L28-31), and the intercysteine fragments disclosed at P26, L32-P27, L2. All of these can be considered specifically disclosed species, and hence the genus is represented by more than one such species.

In the Advisory Action, the Examiner first argues that since the activity limitations are in the alternative, the claimed polypeptide could be one which was recognized by an anti-(mature

PAPP-A2) antibody (activity ii) but did not have anti-(IGFBP-5) proteolytic activity (activity i). We agree.

She also contends that this means that such a claimed polypeptide could have "any biological function". It is true that, <u>taken alone</u>, activity limitation (ii) does not impose a comprehensive structural constraint on the polypeptide. It must have at least one exposed epitope in common with mature PAPP-A2, but the rest of the sequence could differ, and <u>conceivably</u> could import some biological activity unrelated to those of mature PAPP-A2.

However, this argument <u>totally ignores</u> the prior structural limitations. The polypeptide of 12(a) is, of course, identical to mature PAPP-A2. The polypeptides of 12 are "variants", but they are variants with high structural similarity (99% identity!) *to mature PAPP-A2 and would be expected to retain its activity.*

This is obliquely recognized by the Examiner, who says (middle of page 4 of the Advisory Action) that "the limitations recited in i)-iii) are not required for the polypeptide being claimed". (Activity (iii) is no longer recited.)

The reason for including a functional limitation is so that the claim could not possibly encompass a polypeptide which lacked utility. Thus, if the polypeptide variant happened, despite expectations (or through deliberate disablement) to lack the recited proteolytic activity (i), it must still be useful some other way. If it has activity (ii), it can be used as an assay reagent, by virtue of its ability to be recognized by an anti-PAPP-a2 antibody (e.g., it can be labeled and used as an analyte analogue in a competitive immunoassay). Note that both of these recited activities are activities of PAPP-A2 itself.

The Examiner's concern appears to be that the polypeptide could have a significant biological activity not shared by mature PAPP-A2. That activity would have to be the result of the up to 1% of sequence differences permitted by 12(b).

While theoretically possible to achieve, depending on the

nature of the activity, it would not be easy. Moreover, if permitted by our 99% language, it would likewise be permitted by the less stringent 95% language which the Written Description Training Materials consider to be acceptable. In other words, the PTO has decided that it can live with the "risk" that a 5% modification could be engineered to add a new activity.

In view of the Examiner's position, we have added new claim 102, which leaves out the activity limitations, and claim 103, which only recites the proteolytic activity. See also 109.

4. Enablement (OA §16-18)

Claims 12, 18, 19, 75, 83 and 97-99 stand rejected as having a scope allegedly broader than that of the enabling disclosure. Enablement is conceded for polypeptides comprising SEQ ID NO:2 and for fragments of SEQ ID NO:2 *(cp. new claim 108)*.

4.1. While the Examiner seems to believe that the "and/or" makes the claim more difficult to enable, the reverse is true. The polypeptides which meet the structural limitations of claims 12 et seq. need only meet one of functions (i)-(ii), either one of which is sufficient to confer utility.

4.2. The person skilled in the art is given considerable guidance as to where PAPP-A2 can and can't be mutated. PP 26-27 imply that knowledge of critical regions on PAPP-A is relevant to design of derivatives of PAPP-A2. The regions most likely to mediate activity are identified by P52, L3-10:

> The sequence motifs of PAPP-A (Kristensen et al., 1994, Biochemistry 33, 1592-8) are also found in PAPP-A2: The catalytic zinc binding motif and residues of the putative Met-turn are underlined and bolded in both sequences. Lin-notch motifs (LNR1-3) and short consensus repeats (SCR-1-5) are boxed. Cysteine residues are shaded. All cysteines of mature PAPP-A are also found in PAPP-A2. In addition, the secreted from of PAPP-A2 has four cysteine residues (Cys-343, Cys-533, Cys-618, and Cys-1268) with no counterpart in PAPP-A.

See also P57, L17-22. As to what mutations might be tolerated,

there is a detailed discussion of conservative substitution at P39-40.

Even if some polypeptides meeting just the % identity limitation are inoperative, such inoperative mutants are excluded by the activity limitations. See Ex parte Mark, 12 USPQ2d 1904 (BPAI 1989). If, contrary to reasonable expectations, a single conservative substitution in a location outside the taught activity-mediating regions is in fact destructive of functions (i) and (ii), it lies outside the claim.

4.3. With regard to the claims reciting the signal peptide (97), the propropeptide (98), or the prepropeptide (99), these claims have been amended to further recite mature PAPP-A2 or certain disclosed equivalents. Claims 97-99 are thus directed to precursors of *mature* PAPP-A2 *(or close variants thereof)*, and have utility, even if themselves lacking *either* of functions (i) *and* (ii), as intermediates in the production of PAPP-A2 *(or said variants)*.

That said, now that *the polypeptides of* claims 97-99 *include* the mature PAPP-A2 sequence *in (II)(a)*, they should at the very least encompass one or more linear epitopes of PAPP-A2 and thereby satisfy function **(ii)**. *The same is likely to be true of the "95%" variants of (II)(b).*

It is by no means impossible that they further satisfy function **(i)**, as fusion proteins comprising an enzyme moiety and a carrier moiety are known to retain the activity of the original enzyme.

In view of the amendment of claims 97-99, the coverage of the preproPAPP-A2 has been excised from claim 12.

4.4. At page 4 lines 9-13, of the advisory action, the Examiner states

> *Also, it is noted that claims 97-99 now recite "wherein said polypeptide or a cleavable fragment corresponding to sequence (II) of said polypeptide". Therefore the limitations recited in i)-iii) are not required for the polypeptide being claimed. All that is required is that a fragment of the polypeptide recited in (II) meets those*

> *limitations. As such, the claimed polypeptides may have any function.*

Claim 97 is defining an artificial prepeptide or prepropeptide comprising the signal sequence of (I), and the "mature" (mature PAPP-A2 or recited variant) sequence of (II). While it is conceivable that the (I)-(II) fusion will have proteolytic activity in its own right, it is more likely that (I) will need to be cleaved off, leaving (II) as the active entity. The Examiner has no basis for assuming that the signal peptide (I) will impart a significant new biological function (other than the intended one, of facilitating secretion). Similar arguments apply to claims 98-99.

4.5. In the advisory action, in the paragraph bridging pp. 4-5, the Examiner says

> *In regard to the enablement rejection, it is noted that while the polypeptides of claims 97-99 can have any biological function, the specification does not provide the functions of all the polypeptides claimed. In addition, as indicated above, a genus of proteins which can be recognized by an antibody or compete for binding to a cell surface receptor may potentially have <u>many different biological functions</u>. As indicated above, no teaching has been provided as to the required characteristics in an antibody or receptor such that the protein they bind is 97% sequence identical to amino acids 234-1791 of SEQ ID NO:2 and has proteolytic activity for IGFBP-5. Contrary to Applicant's assertion, being recognized by an antibody or being able to bind an <u>undefined</u> cell surface receptor does not meet the utility requirement since those uses are neither specific and substantial or well established. It would require undue experimentation to determine a specific and substantial use for the claimed polypeptides. Therefore, one cannot reasonably conclude that the claimed invention is fully enabled by the specification.*

The references to activity (iii) (re binding to cell surface

receptor) are mooted by the rewording of this amendment relative to the after-final amendment.

Taking up the last point first, we are not asserting that the polypeptides of (ii) are recognized by <u>any</u> antibody, but rather that they are recognized by an anti(PAPP-A2) antibody. Since the examiner has conceded that PAPP-A2 has utility, it follows that an immunologically cross-reactive antigen has utility, as it can be used (in labeled or insolubilized form) as a competitive assay reagent.

Turning to the third sentence of the quoted passage, the claim is to the PAPP-A2 variant, not to the antibody. Hence, we don't have to disclose how to identify the required characteristics of the antibody for binding to the PAPP-A2 variant. With regard to the characteristics of the variant for recognition by an anti-(PAPP-A2) antibody, we already disclose the sequence of mature PAPP-A2 as well as methodology for the prediction of epitopes, see page 40. As a practical matter, even a maximal truncation mutant which is "merely" 99% identical to 12(a) is going to have (99% of 1558 =) 1543 residues in common with mature PAPP-A2. Since many epitopes are linear, and as short as 5-6 residues, it is hard to believe that even one, let alone a significant number, of these mutants will altogether lack a PAPP-A2 epitope.

<u>5. Prior Art Issues (OA §§19-23)</u>

Claims 12, 18-19, 75, 90-92 and 96 stand rejected as anticipated by Farr. Claims 12 and 90 are independent in form.

5.1. We first analyze 12. The Examiner appears to believe that Farr's 1624 a.a. PAPP-E polypeptide, aligned with AAs 168-1791 of SEQ ID NO:2, anticipates claim 12 as examined, through the combined workings of clauses (e) ("at least 97% identical to ...(b)...") and (b) ("consists of residues 234-1791 of SEQ ID NO:2"). *As a result of the present amendment, clause (a) ("comprises SEQ ID NO:2) has been excised (cp. amendments to claim 99) and hence (b) has been redesignated as (a). In*

addition, (c) and (d) were deleted, and (e) redesignated as (b). The new nomenclature will be used from now on.

The flaw in the Examiner's reasoning is that she uses an improper method of calculating % identity.

In essence, she calculates % identity as

$$\frac{\text{number of matches}}{\text{length of shorter (PAPP-A2) sequence}} = \frac{1554}{1558} = 99.7\%$$

(The four mismatches are said to be at AAs 447, 846, 1343 and 1739 of SEQ ID NO:2.)

However, this totally ignores that portion of Farr's PAPP-E which corresponds to AAs 168-233 of SEQ ID NO:2.

We believe that percentage identity should be calculated over the length of the <u>longer</u> sequence, with endgaps counted as mismatches. If so, then the % identity is

$$\frac{\text{\# of matches}}{\text{length of longer (PAPP-E) Seq}} = \frac{1554}{1624} = 95.7\%$$

which of course is <u>less</u> even than 97%, let alone 99% now recited in 12.

We therefore turn to the specification to see what it teaches as to the correct method of calculating % identity.

There is no formal definition of percentage identity, and hence a definition must be inferred. Relevant text includes:

<u>P4, L23-24</u>: "The mature portion of PAPP-A2 is homologous with the mature portion of PAPP-A (approx. 45% identity)."

<u>P9, L31-33</u>: "Homology of PAPP-A2 with PAPP-A is evident upon alignment of the two amino acid sequences as shown in Figure 3. PAPP-A2 and PAPP-A share approximately 45% of their amino acid residues."

<u>P35, L5-9</u>: "In one preferred embodiment of the invention there is also provided variants of SEQ ID NO:2, and variants of fragments thereof. Variants are determined on the basis of their

degree of identity or their homology with a predetermined amino acid sequence, said predetermined amino acid sequence being SEQ ID NO:2, or, when the variant is a fragment, a fragment of SEQ ID NO:2."

We were unable to resolve the intended meaning on the basis of the reference to 45% identity at P4, L23-24 or P9, L31-33, the lengths of PAPP-A and PAPP-A2 being too similar.

Turning to P35, L5-9, if the calculation of degree of identity was intended to use the shorter sequence as the denominator, there would be no need to define "variants of fragments" on the basis of identity with a fragment of SEQ ID NO:2, as then % identity with full-length SEQ ID NO:2 would work just as well.

By the Examiner's logic, any subsequence, however small (even one a.a.) of a longer sequence, however large, would be characterized as having 100% identity to the longer sequence. Moreover, any claim of the form "a peptide comprising a sequence at least X% identical to SEQ ID NO:Y" would be anticipated as all 400 possible dipeptides are known in the art and at least one of them would be a subsequence of SEQ ID NO:Y and thus, by the Examiner's logic, 100% identical to SEQ ID NO:Y.

On page 5 of the advisory action, the Examiner argues

> *In view of the fact that the identity recited is in reference to amino acids 234-1791 of SEQ ID NO:2, the calculation should take into account only what is being recited, which in this case is amino acids 234-1791 of SEQ ID NO:2. The region in the polypeptide of Farr et al. which is not corresponding to what is being recited should not be part of the calculation.*

We agree with the Examiner that the reference sequence is mature PAPP-A2 (234-1791 of SEQ ID NO:2). However, one sequence may vary from another not only by simple replacement of amino acids, but also by insertions and deletions (see page 6, lines 17-24 and page 6 line 34 to page 7, line 2).

The term "variants", as used in the discussion of percentage

sequence identity on page 35, must have the same meaning it was given on pages 6-7, i.e., it includes insertion and deletion mutants. This conclusion is buttressed by the observation that there is a further discussion of addition and deletion of amino acids in the paragraph bridging pp. 36-37.

The Examiner's attention is also directed to the last paragraph on page 37:

> *Functional equivalents or variants of PAPP-A2 will be understood to exhibit amino acid sequences gradually differing from the preferred predetermined PAPP-A2 sequence, as the number and scope of insertions, deletions and substitutions including conservative substitutions increases. This difference is measured as a reduction in homology between the preferred predetermined sequence and the fragment or functional equivalent.*

Thus, in calculating percentage identity with mature PAPP-A2 (residues 234-1791 of SEQ ID NO:2) it is necessary to take into account the addition of residues (as in the case of the N-terminal of PAPP-E) and not just the deletion or substitution of residues. And that is why we need to put the length of the longer (PAPP-E) sequence (in the denominator).

We are not proposing that the examiner align residues 1-66 of PAPP-e with residues 168-233 of SEQ ID NO:2, and count both matches and mismatches. That would make PAPP-E the referent. Rather, we are asking that the examiner recognize that residues 1-66 of PAPP-E are not present in the reference sequence (mature PAPP-A2) and hence must be counted as mismatches.

We would be willing to consider inserting an explicit formula for calculating percentage identity into claim 12, if the Examiner thought that was desirable, and we could reach agreement as to the formula.

5.2. A further issue, not previously addressed by us or by the Examiner, is that Farr discloses a 1542 AA polypeptide corresponding to residues 250-1791 of our SEQ ID NO:2, and further differing from it by the four mismatches previously

identified by the Examiner. It is referred to in the Farr abstract and table 1, and corresponds to residues 1-1542 of the mature PAPP-E sequence set forth in Farr Fig. 1 (the 1624 a.a. Farr sequence is thus preproPAPP-E). If so, then we must consider whether this 1542 AA sequence anticipates claim 12 as amended.

12(a) recites residues 234-1791 of SEQ ID NO:2, not 250-1791, so 12(a) is not anticipated. What about 12(b)? The Farr 1542 AA polypeptide differs from 12(a) on account of (1) residues 234-249 of SEQ ID NO:2 (omitted by Farr) and (2) the four internal mismatches identified by the examiner. That is a total of 20 mismatches, and the longer sequence is SEQ ID NO:2, so the % identity is 1538/1558 = 98.716%.

*That being the case, we have revised claim 12 to recite at least **99%** identity, for which there is basis at P35, L18.*

5.3 According to the final rejection, Farr teaches fragments which anticipate claims 90-92 and 96 as then presented.

Farr's fragments are characterized by the examiner as follows:

	SEQ ID NO:2
SCR-1 (PAPP-E)	1396-1549
SCR-2 (PAPP-E)	1464-1521
SCR-3 (PAPP-E)	1525-1590
SCR-4 (PAPP-E)	1595-1646
SCR-5 (PAPP-E)	1653-1729
LNR-1 (PAPP-E)	586-611
LNR-2 (PAPP-E)	612-644
Zinc-binding motif (PAPP-E)	733-743

Note that by earlier analysis, the mismatches between PAPP-E and PAPP-A2 are at AAs 447, 846, 1343, 1739.

Applicants have amended claim 90 by incorporating the

limitations of claim 94, which was not rejected over the prior art. Hence, the rejection of claim 90 is moot. *The advisory action apparently agrees (see 5.4 below).*

5.4. We thank the Examiner for indicating in the advisory action that amended claims 70, 87, 90-93, 95-96 and new claim 101 are patentable over the prior art.

5.5. Claims 97, 98 and 99, in clause (I), require the polypeptide to comprise

amino acids 1-22 of SEQ ID NO:2 (claim 97) (the prepeptide of prepro PAPP-A2)
amino acids 23-233 of SEQ ID NO:2 (claim 98) (the propeptide of prepro PAPP-A2)
amino acids 1-233 of SEQ ID NO:2 (claim 99) (the prepropeptide of prepro PAPP-A2)

Clause (b) allows for modification of the moiety of clause (II), but does not affect the sequence of clause (I).

Farr's prepro PAPP-E does not contain a region identical to amino acids 1-22, 23-233 or 1-233 of SEQ ID NO:2. This is proven by the alignment attached to the office action of February 10, 2004, where Farr AAs 1-1624 (i.e., prepro PAPP-E) is aligned with residues 168-1791 of SEQ ID NO:2.

*Hence, in each of claims 97-99, clause (II)(b) adopts the minimum percentage identity figure of **95%**, which has basis at P35, L16 and is within the Written Description Training Materials "safe haven".*

5.6. New claim 101 was presented in the non-entered "after final" amendments, and approved by the advisory action.

6. Allowable Claims (OA §24)

We thank the Examiner for indicating in advisory action §8 that upon entry of the amendments corresponding to those proposed January 5, amended claims 70, 87, 90-93, 95-96 and new claim 101 are allowable if rewritten in independent form. Claim 70 has been cancelled, in favor of new claim 109.

§10 additionally identifies claims 85 and 94 as allowable.

Claim 85 was directed to a polypeptide of claim 12 which comprised mature PAPP-A2. The only such polypeptide was the polypeptide of (a), which comprised preproPAPP-A2 (SEQ ID NO:2). Claim 85 has been cancelled because the coverage of preproPAPP-A2 has been transferred from claim 12 to claim 99. New claim 101 is directed to SEQ ID NO:2.

Respectfully submitted,

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